Sofosbuvir (Sovaldi™) and Ledipasvir/Sofosbuvir (Harvoni™)

Criteria for Use

February 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.** *The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or http://vaww.pbm.va.gov for further information.*

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive sofosbuvir-based regimen without local adjudication.*

☐ Limited Life Expectancy (refer to issues for consideration)

☐ Patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis.

☐ Patients who have failed prior treatment with NS5a inhibitors (i.e. ledipasvir, ombitasvir, or daclatasvir) (applies to LDV/SOF but not to SOF alone)

☐ Documented ongoing nonadherence to prescribed medications or medical treatment, failure to complete hepatitis C virus (HCV) disease evaluation appointments and procedures or unable to commit to scheduled follow-up/monitoring for the duration of treatment

☐ Known hypersensitivity to any component of the planned treatment regimen

☐ HCV **genotype 2** infection (applies only to LDV/SOF)

Drug interactions

☐ For sofosbuvir, coadministration with rifampin, rifabutin, rifapentine, St. John's wort, anticonvulsants (i.e., carbamazepine, phenytoin, phenobarbital, oxcarbazepine) or tipranavir/ritonavir

☐ For ledipasvir/sofosbuvir, coadministration with rifampin, rifabutin, rifapentine, St. John's wort, carbamazepine, phenytoin, phenobarbital, oxcarbazepine, elvitegravir/cobicistat/emtricitabine/tenofovir, tipranavir/ritonavir, simeprevir, or rosuvastatin.

When a sofosbuvir-containing regimen is used in combination with peginterferon and/or ribavirin

☐ Any contraindications and/or intolerance to peginterferon or ribavirin if sofosbuvir-containing regimen to be used in combination with peginterferon and/or ribavirin

- Contraindication and/or intolerance to ribavirin: Contraindication is defined as history of significant or unstable cardiac disease, known pregnancy, positive pregnancy test, and men whose female partner is pregnant or plan to become pregnant, known hypersensitivity reaction, autoimmune hepatitis, hemoglobinopathies) and/or intolerance (i.e. baseline hemoglobin <12g/dL) and/or history of *significant* adverse events with previous ribavirin-containing regimen. **Please note that history of anemia related to ribavirin-containing regimen should be evaluated in context of PBM CFU for ESA (i.e., ribavirin dose reduction to 600mg must have been instituted prior to consideration of ESA use) and does not necessarily constitute intolerance.

☐ Known pregnancy, positive pregnancy test, or men whose female partners are pregnant or plan to become pregnant (if applicable on ribavirin)

Inclusion Criteria *The answers to ALL OF THE FOLLOWING must be fulfilled in order to meet criteria.*

☐ Under care of and/or in collaboration with an experienced VA HCV practitioner

☐ Adherence counseling performed including laboratory follow-up and documented understanding by patient

☐ Treatment regimen and duration based upon HCV Genotype and patient characteristics according to the dosage and administration section below

For women of childbearing potential receiving ribavirin or who have a male partner receiving ribavirin:

☐ When ledipasvir/sofosbuvir or sofosbuvir is used in combination with ribavirin therapy (which is pregnancy category X), the ribavirin should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with sofosbuvir and concomitant ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.

Dosage, Administration

Treatment regimen and duration are based upon patient characteristics as described in the Table below**.**

Ledipasvir/sofosbuvir regimen (i.e., two-drug fixed-dose combination product)

One tablet (90mg of ledipasvir and 400mg of sofosbuvir) taken orally once daily with or without food

Sofosbuvir and ribavirin regimen

Sofosbuvir 400mg orally once daily with or without food in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day).

Sofosbuvir, peginterferon, and ribavirin regimen

Sofosbuvir 400mg orally once daily with or without food *plus* peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) in combination with ribavirin (in 2 divided doses) with food (<75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day)

Population includes patients with HCV monoinfected, HCV/HIV-1 co-infected, or hepatocellular carcinoma (HCC)[a]	**Dosage Regimens**	**Total treatment duration**
HCV Genotype 1		
Treatment-naïve without cirrhosis		
HCV RNA <6 million IU/mL	Ledipasvir/sofosbuvir	8 weeks
HCV RNA ≥6 million IU/mL	Ledipasvir/sofosbuvir	12 weeks
Treatment-naïve with cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[b] without cirrhosis	Ledipasvir/sofosbuvir	12 weeks
Treatment-experienced[b] with cirrhosis[c]	Ledipasvir/sofosbuvir	24 weeks
	OR	
	Ledipasvir/sofosbuvir and ribavirin	12 weeks
Decompensated cirrhosis[c]	Ledipasvir/sofosbuvir and ribavirin (initiate ribavirin at 600mg/day and titrate up as tolerated)	12 weeks
	OR	24 weeks
	Ledipasvir/sofosbuvir (if unable to tolerate ribavirin)	
HCV Genotype 2	Sofosbuvir plus ribavirin	12 weeks
HCV Genotype 3[c]	Sofosbuvir plus ribavirin	24 weeks
	Sofosbuvir plus peginterferon and ribavirin	12 weeks
	Ledipasvir/sofosbuvir plus ribavirin (except for treatment-experienced cirrhotics)	12 weeks
HCV Genotype 4, 5, or 6[c]	Sofosbuvir plus peginterferon and ribavirin	12 weeks
	Ledipasvir/sofosbuvir	12 weeks

[a]Refer to Issues for Consideration for alternative treatment options including patients with decompensated cirrhosis, and pre- and post-transplant.
[b]In clinical trials, treatment-experienced was defined as previous peginterferon/ribavirin with or without an NS3-4a protease inhibitor
[c]Refer to Issues for Consideration for additional information

Recommended Monitoring

In addition to standard clinical and laboratory monitoring in a patient receiving HCV therapy, the following monitoring is recommended for sofosbuvir-based regimen:

- **Hematologic adverse events (anemia) if co-administered with ribavirin:** Complete blood count with white blood cell differential counts should be obtained at baseline and at treatment weeks 2, 4, 8, and 12, and at other time points, as clinically appropriate. Initial management of anemia should consist of ribavirin dose reduction for hemoglobin <10g/dL or sooner if clinically indicated; for additional monitoring and management of Hepatitis C treatment-related anemia refer to the PBM CFU for Recombinant Erythropoietin.
- Virologic monitoring **should be assessed to determine response to treatment. Patients receiving any sofosbuvir-based regimen should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.**

- **Sustained Viral Response (SVR) or non-response** should be determined by measurement of HCV RNA at 12 weeks after stopping treatment.
- **Ongoing assessment of treatment adherence** including medical appointments, laboratory follow-up and medications should be performed.
- **Monthly pregnancy tests** for women of childbearing potential receiving ribavirin

Issues for Consideration

Treatment Considerations:

- Refer to separate PBM CFU for sofosbuvir in combination with simeprevir
- **In genotype 1 patients who are treatment-naïve without cirrhosis,** the difference in SVR between subjects receiving 8 weeks of ledipasvir/sofosbuvir and 12 weeks of ledipasvir/sofosbuvir was –2.3% (97.5% CI –7.2% to 2.5%). Among subjects with a baseline HCV RNA <6 million IU/mL, the SVR was 97% (119/123) with 8 weeks of ledipasvir/sofosbuvir and 96% (126/131) with 12 weeks of ledipasvir/sofosbuvir.
- **In genotype 1 patients who had previous virological failure with an NS3-4A protease inhibitor,** ledipasvir/sofosbuvir has been shown to be effective. A 12 week regimen is FDA-approved for non-cirrhotic subjects who have failed prior HCV treatment (including regimens with a protease inhibitor) and 24 weeks of ledipasvir/sofosbuvir is FDA-approved regimen for cirrhotic subjects who have failed prior treatment. However, in a randomized, double-blind study comparing ledipasvir/sofosbuvir plus ribavirin for 12 weeks to ledipasvir/sofosbuvir for 24 weeks in cirrhotic patients who had previously failed NS3-4A protease-inhibitor based triple therapy with boceprevir or telaprevir; SVR was achieved in 96% (74/77) of patients treated with ledipasvir/sofosbuvir plus ribavirin for 12 weeks and in 75/77 (97%) of patients treated with ledipasvir/sofosbuvir for 24 weeks.
- **In genotype 1 patients who had previous virological failure with a sofosbuvir-based regimen,** in a Phase II trial of GT1-infected patients (29% of whom had cirrhosis) who initially failed SOF + PEG-IFN + RBV (n=25) or SOF + RBV (n=21), re-treatment with LDV/SOF + RBV for 12 weeks achieved SVR in 100% (25/25) with prior SOF + PEG-IFN + RBV experience and 95% (20/21) with prior SOF + RBV experience.
- **In genotype 2 patients**, ledipasvir/sofosbuvir has not been studied and therefore, cannot be recommended at this time.
- **In genotype 3 patients**, in vitro, ledipasvir has minimal efficacy against HCV genotype 3. However, ledipasvir/sofosbuvir with or without ribavirin for 12 weeks was evaluated in an open-label study of 51 treatment naïve HCV genotype 3 patients. SVR rates were 100% (26/26) and 64% (16/25) in patients who received ledipasvir/sofosbuvir with and without ribavirin, respectively. In treatment experienced genotype 3 patients, ledipasvir/sofosbuvir plus ribavirin for 12 weeks resulted in SVR rates of 73% (16/22) and 89% (25/28) in those with and without cirrhosis, respectively. **This regimen is not FDA approved**. In a Phase ll open-label study of GT3 treatment-experienced patients treated with sofosbuvir, peginterferon, and ribavirin for 12 weeks, SVR occurred in 83% (10/12) of patients without cirrhosis and 83% (10/12) of those with cirrhosis. **This regimen is not FDA approved.**
- **In genotype 4, 5, or 6 patients,** ledipasvir/sofosbuvir for 12 weeks was evaluated in 25 patients with HCV genotype 6 infection who were mostly treatment naïve (23/25) and non-cirrhotic (23/25); SVR was achieved in 96% (24/25). In genotype 4 patients who were treatment naïve and treatment experienced with peginterferon plus ribavirin, SVR was achieved in 95% (19/20). **This regimen is not FDA approved.**
- **Populations Unlikely to Benefit from HCV Treatment:** According to AASLD/IDSA HCV Guidelines, "patients with limited life expectancy for whom HCV therapy would not improve symptoms or prognosis do not require treatment. Chronic hepatitis C is associated with a wide range of comorbid conditions. Little evidence exists to support initiation of HCV treatment in patients with limited life expectancy (less than 12 months) due to non–liver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized, and palliative care strategies should take precedence."
- **Chronic HCV-infected patients with minimal fibrosis** (METAVIR stage 0 or 1 based on an adequate liver biopsy specimen) and no other risk factors for liver disease are at lower risk for developing advanced liver disease in the short-term. After a thorough discussion of prognosis and treatment options, the provider and patient may agree to observation and defer treatment. Treatment should be reconsidered if liver disease progresses. Modifiable risk factors for progression of liver disease, such as alcohol use, should be addressed.

Use in Specific Populations (refer to Prescribing Information for comprehensive list of use in specific populations):

- **HIV:** Co-infected patients should be managed in consultation with an experienced HIV provider.
- **Decompensated cirrhosis:**
    - In Genotype 1 and 4 patients, ledipasvir/sofosbuvir plus ribavirin (ribavirin initiated at 600mg and titrated upwards as tolerated) for 12 and 24 weeks has been evaluated in patients with Child Pugh B and C decompensated cirrhosis. SVR rates for those with Child Pugh B treated for 12 and 24 weeks were 87% (26/30) and 89% (24/27) respectively. SVR rates for those with Child Pugh C treated for 12 and 24 weeks were 86% (19/22) and 90% (18/20) respectively. Due to safety concerns, patients with decompensated liver disease should not receive a regimen containing peginterferon and/or a NS3-4A protease inhibitor. **Treatment of patients with decompensated cirrhosis should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**
    - In Genotype 2, 3, 5 and 6 patients, limited/no data exists and **care should be managed by physicians with extensive experience in the treatment of patients with advanced liver disease**.
- **Hepatocellular Carcinoma (HCC) or other cancer:** It is reasonable to treat HCV in any patient with HCC or other malignancy *if there is a high likelihood that the cancer has been cured*. Curative treatments for solitary or early stage HCCs within Milan criteria include resection and thermal ablation as well as liver transplantation (TACE, radioembolization, radiation therapy and targeted/chemotherapy are NOT considered curative). For those receiving resection or thermal ablation, if staging studies indicate good likelihood of success (absence of macrovascular invasion, clear margins, etc.) and if follow-up restaging studies show no evidence of cancer recurrence, then treatment of HCV should be offered.

- **Hepatic Impairment:**
  - Ledipasvir/sofosbuvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
  - Sofosbuvir: No dosage adjustment is necessary for patients with mild, moderate or severe hepatic impairment.
- **Pre-liver transplant (also see decompensated cirrhosis and HCC bullet above): <u>The decision to treat *any* patient awaiting transplantation should be made in consultation with the transplant center where the patient is listed and determined on a case by case basis</u>**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation (pre- or post-) or whether treatment is appropriate given patient's prognosis.
- **Post-liver transplant:**
  - In Genotypes 1 and 4, ledipasvir/sofosbuvir plus ribavirin for 12 and 24 weeks was evaluated in post-liver transplant patients with stage F0-F3 disease, Child-Pugh A, B or C disease. SVR in patients without cirrhosis (METAVIR F0 – F3) was 96-98% with ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks. Among patients with cirrhosis, the SVR rates with Child-Pugh A was 96%, 83-85% for Child-Pugh B, and 60- 67% for Child-Pugh C with ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks, respectively.
  - In Genotypes 1, 3, and 4, sofosbuvir plus ribavirin for 24 weeks has been evaluated in two small Phase II trials of post-transplant patients with HCV. In one trial, SVR was achieved in 77% (31/40) of post-transplant patients. In the other trial (a compassionate use program), SVR was achieved in 60% (19/32) in patients receiving sofosbuvir and ribavirin and 50% (6/12) in patients receiving sofosbuvir, ribavirin and peginterferon. Because of the severity of the HCV disease in the patients at the time of treatment initiation, 15 patients died of progressive liver disease during the treatment period.
  - In Genotype 2, 5 and 6, no data exist though responses with sofosbuvir plus ribavirin are expected to be similar to those observed with other genotypes. The decision to treat these patients should be discussed and managed in coordination with the transplant center.
  - **Any sofosbuvir-based regimen should only be used in patients who are being actively managed by physicians with extensive experience in the treatment of post-transplant patients**. Close collaboration with the patient's transplant center is necessary to determine the timing of treatment initiation.
- **Renal Impairment:**
  - Ledipasvir/sofosbuvir: No dosage adjustment is necessary for patients receiving ledipasvir/sofosbuvir with mild or moderate renal impairment; the fixed-dose combination was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis.
  - Sofosbuvir: No dosage adjustment is necessary for patients receiving sofosbuvir with mild or moderate renal impairment; sofosbuvir was not studied in patients with severe renal impairment (eGFR<30mL/min/1.73m^2), end-stage renal disease or on hemodialysis. The major metabolite of sofosbuvir is renally excreted and will accumulate in subjects with eGFR <30 mL/min/1.73m^2.
- **Substance or Alcohol Use:** All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C . Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and is strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation.
- **Mental Health Conditions:** HCV-infected patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder), as documented by psychiatric evaluation, who are engaged in mental health treatment should be considered for therapy on a case-by-case basis. The use of interferon-containing regimens is associated with worsening of these conditions. Patients should be managed in collaboration with Mental Health providers to determine the risks versus benefits of treatment and potential treatment options.
- **Hepatitis B:** No safety and efficacy data are available in this population; prescribing information states that no dosage adjustments are needed for sofosbuvir or ledipasvir/sofosbuvir for patients receiving tenofovir, entecavir or lamivudine.

Drug-interactions:

- Consult the prescribing information prior to use of sofosbuvir-based regimen for potential drug interactions
  - Both ledipasvir and sofosbuvir are substrates of drug transporter P-gp and breast cancer resistance protein (BCRP); drugs that are potent P-gp inducers in the intestine (e.g., rifampin, St. John's wort) may significantly decrease sofosbuvir and ledipasvir plasma concentrations.
  - Ledipasvir is an inhibitor of the drug transporter P-gp and BCRP and may increase intestinal absorption of coadministered substrates for these transporters.
- Drugs that increase gastric pH are expected to decrease absorption and blood concentration of ledipasvir.
  - Separate antacids and ledipasvir/sofosbuvir administration by 4 hours.
  - H2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40mg twice daily
  - Proton-pump inhibitor doses comparable to omeprazole 20mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions

Education and Screening:

- Counsel patient on general liver health, especially abstaining from alcohol use and limiting acetaminophen use to 2g/day.
- Assess if patient previously screened and/or vaccinated for Hepatitis A and Hepatitis B vaccines; consideration vaccination if

appropriate.

- Assess if patient previously screened for HIV; if not, consider testing for HIV.

Additional Resources:

- Refer to VA Office of Public Health Intranet Site http://vaww.hepatitis.va.gov

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